REMARKS

Prior to the present amendment, claims 10, 11, 27 and 63 were pending and claims 1-9, 12-26, and 28-62 were cancelled by the Preliminary Amendment dated December 3, 2003. By this amendment, applicants have cancelled claims 10, 11, 27 and 63 and added new claims 64-72. Accordingly, claims 64-72 are currently pending.

Applicants wish to thank Examiner Rawlings for the courtesy of a personal interview with the undersigned held at the Patent and Trademark Office on September 10, 2003 in connection with the Office Action dated June 3, 2003 for the parent case, U.S. Application Serial No. 09/823,277. A response to the Office Action was not filed in U.S. Application Serial No. 09/823,277. Instead, applicants filed the instant continuation application on December 3, 2003.

In order to facilitate prosecution of the instant application, applicants below address the objections and rejections raised in the Office Action dated June 3, 2003 for the parent case, U.S. Application Serial No. 09/823,277.

In the Office Action dated June 3, 2003, the examiner states that applicants must comply with the Sequence Rules under 37 C.F.R. §§1.821-1.825. Accordingly, applicants submit herewith a disk containing the sequence listing in computer readable form (CRF) and a paper copy of the sequence listing in compliance with 37 C.F.R. §1.821 - 1.825. In addition, this amendment accords SEQ. ID. NOs. to the sequences disclosed throughout the specification. The transmission cover sheet includes a signed statement of equivalence of the CRF on disk and the attached sequence listing as required by 37 C.F.R. §1.821 - 1.825.

In item 6 of the Office Action, the examiner objected to the specification due to formalities. The examiner states that trademarks must be demarcated with the appropriate symbol indicating the proprietary nature and accompanied by generic terminology. Applicants have complied with this requirement by amending the specification accordingly. Therefore, applicants respectfully request that the objection be withdrawn.

Claims 10, 27 and 63 were rejected under 35 U.S.C. §102(b) as allegedly anticipated by Duke-Cohan et al. (*Blood* 1993, 82:2224-2234). According to the examiner, Duke-Cohan et al. teach a bispecific antibody that comprises a binding domain that binds to CD26 (i.e., dipeptidyl peptidase IV). The examiner further states that Duke-Cohan et al. teach a composition comprising the purified antibody and PBS. Thus, the examiner contends the Duke-Cohan et al. discloses all the limitations of the claims.

Applicants respectfully disagree. During the personal interview with Examiner Rawlings on September 10, 2003, the scope of the claims was discussed.

Applicants have cancelled claims 10, 11, 27 and 63 and added new claims 64-72. These claims now recite that the claimed bispecific antibody has a binding specificity for a first epitopte, wherein the first epitope is the epitope of a mammalian dipeptidyl peptidase IV recognized by E19 and E26. During the interview, the examiner, questioned whether the bispecific antibody to DPPIV disclosed in Duke-Cohan et al. would recognize the same epitope as E19 and E26.

Applicants submit herewith a Rule 132 Declaration executed by Dr. Wen-Tien Chen, the sole inventor of the above-identified application. In the Chen Declaration, Dr. Chen provides evidence supporting applicant's position that E19 and E26 do not recognize the same epitope of DPPIV as the anti-DPPIV (i.e., anti-CD26) antibody disclosed in Duke-Cohan et al.

Duke-Cohan et al. report the use of a bispecific antibody to CD4 and CD26 to target activated T cells (see first paragraph of discussion section). Thus, the antibody against DPPIV disclosed in Duke-Cohan et al. binds to DPPIV present on activated T cells.

In the Chen Declaration, Dr. Chen states that it is well known to those skilled in the art that DPPIV is also referred to as CD26. Further, Dr. Chen declares that it is well known to those skilled in the art that activated T cells express CD69. See paragraph 10 of the attached Chen Rule 132 Declaration.

Dr. Chen states that the experiment described in exhibit 2 was performed to determine whether the epitope recognized by monoclonal antibodies E19 and E26 (both directed to DPPIV) are present on $CD69^+$ T cells (see paragraph 10 of the Chen Declaration). Monoclonal antibodies E19 and E26 are recited in the specification and claims.

In the experiment described in exhibit 2, cells were isolated from bone marrow. The isolated cells were characterized by staining with fluorescently labeled antibodies to human CD69, control monoclonal antibody E3 (directed against DPPIV), and monoclonal antibody E19. After labeling, the cells were examined by fluorescent microscopy (see paragraph 11 of the Chen Declaration).

Dr. Chen states that, similar to that reported in Duke-Cohan et al., Figure 1A of exhibit 2 demonstrates that the control monoclonal antibody E3 (directed against DPPIV) bound to activated ($CD69^+$) T cells. Therefore, the control monoclonal antibody E3 directed against DPPIV recognized DPPIV present on $CD69^+$ T cells. See paragraph 12 of the Chen Declaration.

However, cells stained with monoclonal antibody E19 (directed against DPPIV) revealed a staining pattern different from that observed for monoclonal antibody E3 (see above paragraph). Unlike monoclonal antibody E3, monoclonal antibody E19 did not bind to $CD69^+$ T cells (see paragraph 13 of the Chen Declaration and figures 1B and 1C of exhibit 2). In addition, cells recognized by monoclonal antibody E19 were not recognized by anti-CD69 antibodies. Thus, the epitope recognized by E19 is not present on $CD69^+$ T cells.

Therefore, Dr. Chen concludes that monoclonal antibody E19 recognizes an epitope of DPPIV not present on activated ($CD69^+$) T cells (see paragraph 13 of the Chen Declaration). Dr. Chen also declares in paragraph 14 that similar results were obtained for monoclonal antibody E26. Specifically, the epitope recognized by E26 is not present on $CD69^+$ T cells. Therefore, monoclonal antibody E26 recognizes an epitope of DPPIV not present on $CD69^+$ T cells.

Applicant has provided data demonstrating that monoclonal antibodies E19 and E26 do not bind $CD69^+$ T cells (i.e., activated T cells). As mentioned above, unlike monoclonal

antibodies E19 and E26, the monoclonal antibody to E3 and the monoclonal antibody to DPPIV in the cited art bind to activated (i.e., $CD69^{+}$) T cells. Therefore, the epitope recognized by monoclonal antibodies E19 and E26 are different from the epitope recognized by the monoclonal antibody E3 and the monoclonal antibody to DPPIV in the cited reference. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §102(b) be withdrawn.

Claims 10, 11, 27 and 63 were rejected under 35 U.S.C. §103(a) as allegedly obvious over U.S. Patent No. 5,545,405 in view of U.S. Patent Nos. 6,193,968 and 5,753,230, Cheng et al. (*J. Biol. Chem.* 1998, 273:24207-24215), Johnson et al. (*J. Cell Biol.* 1993, 121:1423-1432), Arao et al. (*Pancreas* 2000, 20:129-137), Masumoto et al. (*Hepatology* 1999, 29:68-74), Klominek et al. (*International J. Cancer* 1997, 72:1034-1044), Lundstrom et al. (*Biochem Biophys Res. Comm.* 1998, 250:735-740), Fukushima et al. (*Internat. J. Cancer* 1998, 76:63-72), Abdel-Ghany et al. (*Invasion & Metastasis* 1998, 18:35-43) and Elble et al. (*Current Topics in Microbiology and Immunology* 1996, 213:107-122).

The examiner states that the '405 patent discloses a method for treating cancer by administering a bispecific antibody. The examiner concedes that the '405 patent does not teach a bispecific antibody that binds specifically to an epitope of dipeptidyl peptidase IV or CD26, and to an epitope of seprase, MT1-MMP, MMP-2 or $\alpha 3\beta 1$-integrin.

To rectify the deficiency, the examiner cites the secondary references. The examiner states that it would have been *prima facie* obvious to use a bispecific antibody the binds dipeptidyl peptidase IV and $\alpha 3\beta 1$-integrin in practicing the '405 patent. The examiner reasons that because the '968, '230 and '941patents teach an antibody that binds to a $\beta 1$ integrin to inhibit cancer cell invasion and angiogenesis, while the Arao et al., Masumoto et al. Klominek et al., Lundstrom et al. and Fukushima et al. provide evidence that antibodies to $\beta 1$ integrin can block adhesion, migration and invasion of malignant cells, and Cheng et al., Johnson et al., Abdel-Ghany et al. and Elble et al. teach the role of dipeptidyl peptidase IV in metastasis by blocking adhesion, migration and invasion.

Applicants respectfully disagree that the claimed invention is obvious over the cited references. During the personal interview, limitations to the base claim were discussed.

The claims have been amended to recite that the claimed bispecific antibody has a binding specificity for a first epitopte, wherein the first epitope is the epitope of a mammalian dipeptidyl peptidase IV recognized by E19 and E26. During the interview, the examiner, questioned whether the antibody to DPPIV disclosed in Cheng et al., Johnson et al., Abdel-Ghany et al. and Elble et al. would recognize the same epitope as E19 and E26.

In the Chen Declaration, Dr. Chen provides evidence that monoclonal antibodies E19 and E26 do not recognize the same epitope of DPPIV as the DPPIV antibodies disclosed in Cheng et al., Johnson et al., Abdel-Ghany et al. and Elble et al.

Dr. Chen states in paragraph 16 of the Chen Declaration that the cited references of Cheng et al., Johnson et al., Abdel-Shany et al. and Elble et al. report that DPPIV is an adhesion receptor for fibronectin. Further, the cited art discloses that monoclonal antibodies to DPPIV inhibit binding of DPPIV to fibronectin. The reported inhibition of binding is said to inhibit adhesion and spreading of cells.

Dr. Chen states in his Rule 132 Declaration that he investigated the ability of monoclonal antibodies E19 and E26 (directed against DPPIV) to inhibit spreading and attachment of W138 human embryonic fibroblasts on a fibronectin-coated collagen substratum (see paragraph 16 of the Chen declaration).

Human embryonic fibroblasts cells W138 were seeded, coated with rat tail type I collagen, and further coated with bovine serum fibronectin. The W138 cells were seeded with monoclonal antibody E19 (directed against DPPIV), ngative control monoclonal antibody C37 (directed against gp-90) and positive control monoclonal antibody C27 (directed against β1 integrins). See paragraph 17 of the Chen Declaration.

As expected, the negative control monoclonal antibody C37 (anti-gp-90) did not inhibit cell spreading and adhesion. However, also as expected, the positive control monoclonal antibody C27 (β1 integrins) inhibited W138 cell spreading and adhesion on fibronectin-coated collagen substratum. See paragraph 18 of the Chen Declaration.

Figure 2A and 2B of exhibit 3 demonstrate that addition of monoclonal antibody E19 did not inhibit cell spreading and attachment. Therefore, the data indicates that monoclonal antibody E19 does not inhibit binding of DPPIV to fibronectin. See paragraph 19 of the Chen Declaration.

Similar results were obtained for monoclonal antibody E26. Specifically, monoclonal antibody E26 did not inhibit cell spreading and attachment of W138 cells on fibronectin-coated collagen substratum. Therefore, monoclonal antibody E26 does not inhibit binding of DPPIV to fibronectin. See paragraph 20 of the Chen Declaration.

Applicant has provided data demonstrating that monoclonal antibodies 19 and E26 do not inhibit binding of DPPIV to fibronectin. Unlike monoclonal antibodies E19 and E26, the antibodies to DPPIV in the cited references inhibit binding of DPPIV to fibronectin. Thus, the epitope recognized by E19 and E26 differs from the epitope recognized by anti-DPPIV antibodies in the cited references.

Therefore, a bispecific antibody with binding specificity for a first epitope wherein the first epitope is the epitope of a mammalian dipeptidyl peptidase IV recognized by E19 and E26 would not be obvious and would not be within the skill of one in the art.

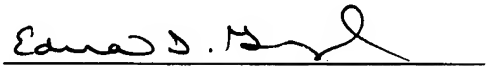
Applicants have provided arguments to refute the rejection of claims 10, 11, 27 and 63 over Cheng et al., Johnson et al., Abdel-Shany et al. and Elble et al. cited by the examiner. The other references cited by the examiner, namely the '405 patent, discloses a method for treating cancer by administering a bispecific antibody, and the '968 patent, '230 patent, '941 patent, Arao et al., Masumoto et al., Klominek et al., Lundstrom et al. and Fukushima et al., disclose

antibodies with binding specificity to other epitopes, such as integrins. Therefore, these other references cannot sustain the rejection.

Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §103(a) be withdrawn.

In view of the above amendments and remarks, applicants respectfully request allowance of pending claims 64-72, which is earnestly requested. If the examiner has any questions regarding this amendment, the examiner is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,



Edna I. Gergel, Ph.D.
Registration Number 50,819
Agent for Applicant

HOFFMANN & BARON, LLP
6900 Jericho Turnpike
Syosset, New York 11791
Tel. (516) 822-3550
Fax (516) 822-3582

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